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# Cerebral Vasoreactivity and Blood Flow Before and 3 Months After Carotid Endarterectomy

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**We measured regional cerebral blood flow and cerebral vasoreactivity before and 3 months after carotid endarterectomy using xenon-133 inhalation with single-photon emission computed tomography and the acetazolamide test in 14 selected patients who had suffered cerebral transient ischemic attacks due to an ipsilateral internal carotid artery stenosis. The patients had neither clinical nor cerebral computed tomographic evidence of infarction. Baseline regional cerebral blood flow was symmetrical before and unchanged after endarterectomy. Before endarterectomy, vasoreactivity in the middle and anterior cerebral artery territories of the symptomatic side was significantly reduced ( $p < 0.05$ ); however, vasoreactivity was normalized 3 months after surgery. Our findings strongly suggest that the stenoses caused a reduction in perfusion reserve that was improved by carotid endarterectomy. (*Stroke* 1990;21:1029–1032)**

**A**lthough carotid endarterectomy is one of the most common vascular operations,<sup>1</sup> its effect on cerebral blood flow (CBF) and intracranial hemodynamics have not been fully clarified.<sup>2–10</sup> The diversity of results presumably reflects differences in studies with regard to patient selection, timing of the postoperative evaluation, and methodology used to measure CBF.

The purposes of our study were to assess regional cerebral blood flow (rCBF) using xenon-133 inhalation and single-photon emission computed tomography (SPECT) and cerebral vasoreactivity using the carbonic anhydrase inhibitor acetazolamide<sup>11</sup> before and 3 months after carotid endarterectomy.

## Subjects and Methods

We studied 14 patients (12 men and two women) aged 52–70 (mean 62) years. They had experienced cerebral transient ischemic attacks (TIA) due to ipsilateral internal carotid artery (ICA) stenosis, and they were treated with carotid endarterectomy. The interval from the last TIA to endarterectomy varied from 10 to 33 (median 15) days. Patients who had a history of stroke, clinical findings suggestive of cere-

bral infarction, or cerebral computed tomographic evidence of infarction were excluded. The patients had experienced no symptoms from the contralateral cerebral hemisphere or the brain stem. This selection was made in order to exclude the effects of cerebral infarction on the rCBF studies. No patient had orthostatic provoked symptoms. The study was performed in accordance with the Helsinki Declaration, and informed consent was given by all patients.

Stenosis was assessed preoperatively using conventional arteriography and pulsed Doppler ultrasound studies.<sup>12</sup> Three stenoses (22%) reduced the diameter of the ICA by 50%–75%, two (14%) by 75%–90%, and the remaining nine (64%) by >90%. Ten stenoses were in the left and the other four were in the right ICA. In the contralateral ICA, a stenosis of <50% was found in three patients, a stenosis of 75% in one patient, and a stenosis of 90% in another; the contralateral ICA was occluded in two patients and normal in the remaining seven (50%). One patient had a vertebral artery stenosis that reduced the diameter by 50%.

Clinical neurologic examination and pulsed Doppler ultrasound studies of the precerebral carotid arteries were repeated 3 months after endarterectomy.

The rCBF studies were carried out 2–15 (median 10) days before and 3 months (median 86 days) after endarterectomy using xenon-133 inhalation and SPECT (Tomomatic 64, Medimatic Inc., Copenhagen, Denmark). Two 2-cm-thick transaxial slices of brain tissue with an unseen interslice distance of 2 cm (slices 2 and 3) were studied. The midslice planes

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TABLE 1. Baseline Regional Cerebral Blood Flow in Patients Before and 3 Months After Carotid Endarterectomy and in Controls

	Patients (n=14)				Controls (n=25)
	Before		After		
	Symptomatic side	Contralateral side	Symptomatic side	Contralateral side 0.7	
Regional cerebral blood flow (ml/100 g/min)					
Anterior cerebral artery	54.4±3.5	55.8±3.3	54.7±3.5	54.4±3.5	55.7±1.2
Middle cerebral artery	57.3±3.4	58.4±3.6	57.1±3.7	56.5±3.5	61.2±1.4
Posterior cerebral artery	53.3±3.3	53.4±3.0	54.1±3.8	53.3±3.5	54.2±1.1
Slice 2	56.0±3.3	56.7±3.4	56.1±3.6	55.4±3.4	56.7±1.7
Slice 3	54.6±3.4	54.9±3.5	55.0±4.2	55.4±4.5	59.2±1.3
PCO <sub>2</sub> (mm Hg)	40.5±1.2		40.5±0.9		40.9±0.7

Data are mean±SEM.

were located 6 and 10 cm above the orbitomeatal plane, respectively. Mean rCBF values were calculated on each side for slices 2 and 3 and for standardized regions of interest in slice 2 corresponding approximately to the perfusion territories of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA).<sup>13</sup> rCBF values were not corrected for PCO<sub>2</sub>. Each study consisted of two measurements. Following a measurement of rCBF at baseline, 1 g i.v. acetazolamide was given and rCBF was measured again approximately 20 minutes later. Cerebral vasoreactivity was calculated as the difference between the two rCBF values.

The patients were compared with 25 healthy controls (13 men and 12 women) aged 23–66 (mean 41) years, 12 of whom had been given acetazolamide.<sup>13</sup> In the controls, rCBF was higher on the right than on the left. Therefore, control values were weighted with regard to the number of endarterectomies performed on the right or left side.

Results are presented in the text as mean±SEM. Student's procedure<sup>14</sup> was used to calculate 95% confidence intervals for baseline rCBF and cerebral vasoreactivity for the controls. One-tailed tests were found to be the most appropriate, and differences were considered significant when  $p \leq 0.05$ . Student's paired  $t$  test was used to compare changes within a

patient. Student's two-sample  $t$  test was used to compare groups. In individual patients, a baseline rCBF or cerebral vasoreactivity was considered to be reduced if asymmetry in a region of interest exceeded the 95% fractile for asymmetry in the controls.

### Results

No patient developed postoperative neurologic complications, and there were no new TIAs during the 3-month observation period. Results of clinical neurologic examination were normal in all patients, and Doppler ultrasound studies revealed no restenoses of the operated ICA 3 months after endarterectomy.

In the patients, end-expiratory PCO<sub>2</sub> during the rCBF measurements did not differ significantly before and after surgery, nor did it differ significantly from that in the controls (Table 1). Acetazolamide significantly reduced PCO<sub>2</sub>, by 3.6±0.5 and 4.0±0.7 mm Hg before and after endarterectomy in the patients, and by 3.1±0.9 mm Hg in the controls. No side effects were observed due to the administration of acetazolamide.

Before endarterectomy, baseline rCBF values in the patients did not differ significantly between sides, nor did they differ significantly from those in the controls (Table 1). Cerebral vasoreactivity values on the symptomatic side were significantly lower than on the contralateral side and than in the controls for the

TABLE 2. Cerebral Vasoreactivity in Patients Before and 3 Months After Carotid Endarterectomy and in Controls

Territory	Patients (n=14)						Controls (n=12)	
	Before			After			Mean	Asymmetry
	Symptomatic side	Contralateral side	Asymmetry	Symptomatic side	Contralateral side	Asymmetry		
ACA	6.6±1.8*†	9.3±2.3	2.7±1.3	10.9±2.3	10.8±2.1	-0.1±0.7	13.5±1.2	0.3±0.7
MCA	9.0±1.5*†	11.6±2.7	2.6±1.7	13.0±2.0	13.6±2.2	0.6±1.0	15.5±1.5	1.0±0.6
PCA	12.7±1.8	13.9±2.1	1.2±0.8	14.2±2.2	14.2±2.2	0.0±1.1	15.3±1.8	-0.6±0.7
Slice 2	9.2±1.7*†	11.8±2.4	2.6±1.3	12.8±2.0	13.2±2.1	0.4±0.6	15.2±1.4	0.5±0.5
Slice 3	9.1±2.0*†	12.5±2.2	3.4±1.4	14.4±1.5	14.5±2.2	0.1	16.8±1.3	0.4±0.6

Data are mean±SEM ml/100 g/min. ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

\* $p \leq 0.05$  different from contralateral side by Student's paired  $t$  test (one-tailed).

† $p < 0.05$  different from controls by Student's two-sample  $t$  test (one-tailed).

ACA, MCA, slice 2, and slice 3 (Table 2); values on the contralateral side did not differ significantly from those in the controls. In the patients, cerebral vasoreactivity in the PCA did not differ significantly between sides ( $p=0.18$ ), and although these values were lower than that in the controls, the differences were not significant.

After endarterectomy, baseline rCBF values did not differ significantly from those before surgery, and they did not differ significantly from those in the controls (Table 1). The preoperative asymmetry of cerebral vasoreactivity in the ACA, MCA, slice 2, and slice 3 was no longer present (Table 2). Cerebral vasoreactivity did not differ significantly between sides, and values did not differ significantly from those in the controls.

Assessment of the results in individual patients showed that two had a reduced baseline rCBF and reduced cerebral vasoreactivity in the MCA and ACA territories on the symptomatic side before endarterectomy. Both patients had an ipsilateral ICA stenosis that reduced the diameter by  $>90\%$ ; the contralateral ICA was occluded in one and normal in the other patient. Three months after endarterectomy baseline rCBF values and cerebral vasoreactivity were symmetrical. Eight patients (57%) had reduced cerebral vasoreactivity in the MCA and/or ACA territories on the symptomatic side before endarterectomy. Six (75%) of these eight patients had a relevant ICA stenosis that reduced the diameter by  $>90\%$ , whereas this was the case for three (50%) of the remaining six patients. The two groups did not differ with regard to atherosclerotic lesions of the contralateral ICA. All 14 patients had symmetrical cerebral vasoreactivity in the MCA and ACA territories 3 months after endarterectomy.

### Discussion

In our study cerebral vasoreactivity in the MCA and/or ACA territories was reduced on the symptomatic side before endarterectomy. Three months after surgery, however, cerebral vasoreactivity in these areas was symmetrical and within normal limits. Similar findings were not present before surgery in the PCA territory, presumably reflecting the relatively greater potential collateral circulation to this area via the vertebrobasilar system.

We uncovered limited/reduced perfusion reserve when attention was paid to asymmetry of cerebral vasoreactivity. By comparing the degree of asymmetry of the response to acetazolamide, the assessment of cerebral vasoreactivity becomes independent of random changes in rCBF and  $P_{CO_2}$ .

Two previous studies have demonstrated the usefulness of the acetazolamide test in assessing the cerebral perfusion reserve before endarterectomy in patients with carotid stenoses.<sup>15,16</sup> These authors found that enhanced asymmetry following acetazolamide administration was highly predictive of reduced stump pressure or reduced cerebral perfusion pressure at the time of endarterectomy.

Schroeder et al<sup>17</sup> used acetazolamide to assess the effect of carotid endarterectomy on cerebral vasodilatory capacity. They measured CBF using the intravenous xenon-133 technique and a mobile unit with 10 fixed detectors. These authors found a clear correlation between the improvement in perfusion reserve, in terms of a change in interhemispheric CBF asymmetry after vasodilatation, and the degree of hemodynamic impairment as evaluated by the ICA/common carotid artery pressure ratio.

Changes in cerebral vasoreactivity following carotid endarterectomy have also been assessed using  $CO_2$  inhalation.<sup>18,19</sup> These studies have provided evidence suggesting decreased cerebral vasoreactivity in patients with severe carotid stenoses. The vasodilatory effect of acetazolamide has been found to be at least as effective as 5%  $CO_2$  inhalation,<sup>20</sup> and this drug offers several advantages over the inhalation of hypercapnic air. Acetazolamide causes no discomfort to the patient, and the systemic arterial blood pressure remains constant. In addition, the cerebral metabolic rate for oxygen remains constant after the administration of acetazolamide.<sup>21</sup> The exact mechanism behind acetazolamide's vasodilatory effect is not known, but a decrease in cerebral pH due to inhibition of carbonic anhydrase in the brain, causing carbonic acidosis, has been suggested.<sup>22</sup>

Two of our 14 patients had decreased baseline rCBF values and reduced cerebral vasoreactivity in the MCA and ACA territories on the symptomatic side before endarterectomy; 3 months after surgery baseline rCBF values and cerebral vasoreactivity were symmetrical in these regions. These findings strongly suggest that the preoperative reduction in perfusion in these two patients was due to a compromised blood supply rather than to permanent ischemic damage. Eight patients (57%) had reduced cerebral vasoreactivity in the MCA and/or ACA territories on the symptomatic side before endarterectomy; 3 months after surgery cerebral vasoreactivity in these regions was symmetrical and within normal limits.

The clinical implications of our findings are at present unclear but may prove to be important with regard to both the assessment of prognosis and the selection of patients for carotid endarterectomy. Our findings suggest that ICA stenosis may impair cerebral hemodynamics more often than suspected from the clinical history alone. Reduced cerebral vasoreactivity implies a compromised collateral circulation and may be of help in recognizing those patients with congenital or atheromatous changes of the collateral channels. In this respect it is of importance that autopsy studies have demonstrated single or multiple anomalies in the most prominent source of collateral blood flow, the circle of Willis, in  $>50\%$  of specimens.<sup>23</sup> Reduced cerebral vasoreactivity may therefore be an early indication of a reduced collateral potential with a subsequently greater risk of developing an ischemic stroke if the carotid stenosis becomes more severe or if the vessel becomes

occluded. There is also evidence suggesting that areas of brain tissue with marginal perfusion may be more susceptible to the effect of microemboli.<sup>3</sup>

Reduced cerebral vasoreactivity may also have implications with regard to endarterectomy itself. It would seem particularly important to carefully monitor blood pressure in these patients and to consider the use of a shunt during endarterectomy. In addition, measures should be taken immediately after surgery to avoid a hyperperfusion syndrome.<sup>24,25</sup>

In conclusion, our study provides evidence suggesting that rCBF measurements using xenon-133 inhalation and SPECT combined with the acetazolamide test may be used to assess the cerebral vasodilatory reserve capacity before and after carotid endarterectomy. Furthermore, carotid endarterectomy improves cerebral vasoreactivity in those patients with a carotid stenosis who have a compromised perfusion reserve. Although the clinical implications of our findings are at present unclear, they may prove to be important when evaluating both the prognosis and the most appropriate treatment for the patient.

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KEY WORDS • acetazolamide • endarterectomy • cerebral blood flow